Editorials

What We See Most, We Understand Least

HIRSUTISM CAN BE DEFINED as the presence of excessive terminal hair in a woman in areas typically associated with male sexual hair growth. It is a sensitive marker for increased androgen action and can be found in combination with other clinical features of hyperandrogenism including acne and male pattern hair loss. The Ferriman and Gallwey score is the conventional and most widely used method to objectively document the degree of hirsutism.[1] We recommend that it be used whenever assessing a patient with hirsutism. Before deciding if a woman has hirsutism, her ethnic origin should be taken into consideration. It should be remembered that a genetic predisposition to the development of terminal hair (because of inherited differences in 5α-reductase activity) varies with ethnic origin. Clearly, what may be considered hirsutism for a Scandinavian woman may well be within the normal limits for a woman from the Middle East or the Mediterranean region.

Androgens are cholesterol-derived C19 steroids that are principally secreted from the ovaries and adrenal cortex. In addition, small amounts may be produced through conversion from other steroids in tissues such as the liver, muscle, and fat. Under normal circumstances, testosterone is the major biologically active circulating androgen, and the vast majority of it in the circulation is bound to sex hormone–binding globulin (SHBG). Because only the free component of a steroid hormone is functionally active, the level of SHBG and, to a lesser degree albumin, can have a profound influence on the activity of testosterone and other androgens. For example, a small decrease in SHBG in the presence of a constant concentration of total testosterone, as found in obesity, can produce a state of clinical hyperandrogenism. Conversely, through hepatic effects, estrogens can increase SHBG and hence lead to a decrease in free testosterone levels. This can be used clinically to treat symptomatic hyperandrogenism.

Due to 5α-reductase activity at the level of the hair follicle, testosterone, androstenedione, and to a lesser extent, other unbound circulating androgens are converted to dihydrotestosterone, a highly potent androgen. This then acts by androgen receptors on the pilosebaceous unit to promote terminal hair growth. Areas of the body that have high levels of 5α-reductase activity are particularly sensitive to the effects of androgens. These normally include the pubic and axillary regions. In the presence of high androgen levels or increased 5α-reductase activity, however, terminal hair growth in other, typically male, areas may ensue. These include the face, chest, lower abdomen, upper thighs, and back. The development of hirsutism, therefore, is dependent not only on the concentrations of free C19 steroids, but also on the degree of 5α-reductase activity and the presence of functioning androgen receptors.

Despite being the most common endocrinopathy of women during the reproductive years, the polycystic ovary syndrome is also the least understood cause of hirsutism. Stein and Leventhal were the first to describe the syndrome of hirsutism, amenorrhea, and obesity in association with sclerocystic ovaries.[2] Since this initial description in 1935, there has been much debate regarding virtually every feature of this syndrome. Even the fundamental aspects, such as its precise definition, are disputed. In reality, it is probable that the polycystic ovary syndrome represents a heterogeneous spectrum of disorders rather than a single disease.

The definition of the polycystic ovary syndrome most prevalent in North America is a clinical one that relies on evidence of chronic anovulation with hyperandrogenism. Although this may be associated with mild elevations in serum prolactin, dehydroepiandrosterone-sulfate (DHEAS), and testosterone concentrations, specific pituitary, adrenal, and ovarian conditions should be excluded before making the diagnosis. It is often helpful to think of the polycystic ovary syndrome as a diagnosis of exclusion, and it should be noted that the appearance of polycystic ovaries is not required. When using this definition, estimates of its prevalence range from 5% to 10%.

The health consequences of the polycystic ovary syndrome are varied and are thought to largely result from either the excess production of luteinizing hormone, androgens, insulin, or unopposed noncycling estrogens. Women with this syndrome may present with a number of complaints including hirsutism, infertility, obesity, irregular bleeding, amenorrhea, recurrent pregnancy loss, acne, and hair loss.

Most women with the polycystic ovary syndrome have an element of insulin resistance. The degree of this resistance is only partly related to the body mass index because even nonobese women with this syndrome can be affected. The resultant hyperinsulinemia has two important effects: there is increased stimulation of ovarian theca cell androgen production by both insulin and insulinlike growth factor receptors, and there is a lowering of SHBG levels. Indeed, the correlation between SHBG levels and the degree of insulin resistance is pronounced. The consequence of these two insulin-mediated effects is to increase the availability of bioactive androgen.

Occasionally women with the polycystic ovary syndrome have mild elevations of adrenal androgen (DHEAS) levels. It can be postulated that in these cases, DHEAS can be used as substrate in the ovary for the production of more potent androgens.

Unopposed estrogenic stimulation of the endometrium can result in endometrial hyperplasia or cancer. Cases of endometrial cancer have been reported in women as young as 17 years and typically occur in obese persons. Furthermore, it has been reported that as many as a quarter of patients with endometrial carcinoma younger than 40 years have the polycystic ovary syndrome. Fortunately, the tumors are invariably well-differentiated adenocarci-

nomas, and because of this, they are usually at an early stage at diagnosis. It is postulated that unopposed estrogen also leads to hyperprolactinemia in about 25% and galactorrhea in 13% of women with the polycystic ovary syndrome.

Other long-term health consequences of the polycystic ovary syndrome include a markedly increased risk for cardiovascular disease, with an estimated 11-fold increased risk of myocardial infarction between the ages of 50 and 61 years. Recent preliminary reports also suggest an increased risk of breast cancer in women with this syndrome.

Because the cause of this common syndrome is unknown, it is not surprising that there is no specific treatment for it. It is clear that because of the many serious health problems attributable to the polycystic ovary syndrome, the management of a patient with this condition requires attention not just to the immediate complaints, but also to the prevention of long-term sequelae. Patient education is of paramount importance if long-term compliance is to be achieved.

In Europe, the antiandrogen cyproterone acetate is one of the most commonly employed treatments of hirsutism associated with the polycystic ovary syndrome. It has progestogenic activity and is combined with ethinyl estradiol in a combined oral contraceptive (Diane). In North America, cyproterone acetate is unavailable, and spironolactone, a mineralocorticoid antagonist with androgen receptor-blocking activity, is used extensively. Flutamide, another antiandrogen, and finasteride, a specific 5α-reductase inhibitor, have been reported to have good effect in the treatment of hirsutism associated with the polycystic ovary syndrome. For the optimal efficacy of spironolactone and flutamide treatments, these drugs are often prescribed with a combined oral contraceptive pill. If oligomenorrhea or amenorrhea is present, the addition of an oral contraceptive pill will also eliminate the increased risk of endometrial cancer. Maximal effects with any of the above forms of therapy take in excess of four months to manifest clinically. Hence, it should be recommended that patients wait at least this long to allow the cessation of new terminal hair growth before undergoing physical forms of hair removal to remove any pretreatment unwanted hair.

Correcting obesity can further augment the therapeutic results. In one long-term noncontrolled prospective study of obese women with the polycystic ovary syndrome, a 5% reduction in body weight led to a decrease in serum insulin and free testosterone levels and a rise in SHBG levels.[3] This group was also substantially more likely to have improvement in reproductive function, as documented by more regular menstrual cycles and improved pregnancy rates, than those women who lost less than 5% of their baseline weight.

The differential diagnosis of hirsutism includes a number of other conditions. Unless the physician specifically explores the possibility of each of these, the correct diagnosis will not be made. For example, treating a woman with the complaints of hirsutism, obesity, and menstrual irregularity with oral contraceptives because of the presumed diagnosis of the polycystic ovary syndrome would not be appropriate if she has the Cushing's syndrome. In this issue of the journal, Roland Sakiyama, MD, presents an overview of the approach to patients with hirsutism.[4] The possible causes, necessary diagnostic evaluation, and treatments are covered in a systematic manner. It is fortunate that most causes of hirsutism are relatively benign. Steroid-secreting tumors are uncommon, even in a reproductive endocrinology clinic setting.

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The Search for Viable Myocardium

LEFT VENTRICULAR FUNCTION is among the most important determinants of long-term prognosis in patients with coronary artery disease.[1] It is now apparent that left ventricular dysfunction does not always represent an irreversible process, as was once thought, but may be reversible, at least in part, in a large subset of patients with coronary artery disease. Left ventricular performance may be reduced on the basis of regionally ischemic, stunned, or hibernating myocardium rather than fibrosis from previous myocardial infarction. The detection of reversibly dysfunctional myocardium is clinically relevant because regional and global left ventricular function in such patients may improve substantially after revascularization. A third or more of patients with chronic coronary artery disease and left ventricular dysfunction manifest a substantial improvement, and even a return to normal, of ventricular function after bypass surgery or angioplasty.[2] This improvement in systolic function, in turn, translates into enhanced survival. Thus, as discussed in the review by Birnbaum and Kloner elsewhere in this issue of the *Journal*,[3] the recognition that many patients with coronary artery disease and left ventricular dysfunction may not have irreversibly damaged ventricles, and the development of cost-effective imaging techniques to